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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,381	09/25/2001	Gary Lynch	1819.0040001/MAC/LBB	7154

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,381	LYNCH ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *9-12,20-35,38-58 and 63-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8,13-19,36,37,59-64 and 69-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election of group I, claims 7, 8, 13-15, 17-19, 63, 64, 69-71, 73 and 74 is acknowledged. Linking claims 1-6, 16, 36, 37, 59-62, 72 and 75 are examined in reference to the elected subject matter Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-8, 13-19, 36, 37, 59-64 and 69-75 are examined in this office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 13-19, 36, 37, 59-64 and 69-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining the effect of a substance on characteristics of Alzheimer's disease in brain cells, does not reasonably provide enablement for any neurodegenerative disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The only disease correlation that the specification shows between APP and integrin is Alzheimer's disease. Further at the time of filing, the art only recognized Alzheimer's disease has having this correlation. In addition, the only guidance provided in the specification is to Alzheimer's disease. The specification provides no guidance as to other characteristics related to other neurological diseases that are modulated by integrins. Only APP, aβ and integrin are taught sufficiently by the specification to provide the guidance needed.

Thus, it would have required an undue amount of experimentation at the time of filing for the skilled artisan to make and use the present invention without having to engage in an undue amount of experimentation lacking a predictable degree of success.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 8, 13, 16-18, 37, 59-61, 63, 64, 69 and 72-74 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

It is noted to applicant that "condition that modulates integrins or integrin receptors" is disclosed in the specification to include A/β peptide (specification, page 19, parag. 0065, lines 1-4).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). In particular Harris-White teaches determining the effect of TGFβ on β-amyloid using the hippocampal slice model where the hippocampal slice is incubated simultaneously in media comprising both TGFβ and β/A (page 10368, col. 2, parag. 1, lines 1-3). Harris-White teaches that isoforms of TGFβ added to hippocampal slice cultures in conjunction with the addition of Aβ resulted in an increase in the amount of A/β within the slice and a 2 to 3-fold increase of control experiments in the number of plaque-like deposits and prolonged the course of cellular Aβ staining (page 10368, col. 2, parag. 4, lines 5-7 and page 10369, col. 2, parag. 1, lines 22-25). Harris teaches detection of the increase in Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ1-

40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Thus, Harris-White clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 6, 36 and 59-62 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Matter et al (1998) Journal of Cell Biology 141, pp. 1019-1030 in view of Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Matter teaches that integrin α5-negative neuroblastoma cells, IMR-324β1, transformed with DNA sequences encoding integrin α5, when incubated with Aβ, resulted in a 5-fold decreased accumulation of Aβ deposits in the cells as compared to non-transformed control cultures (1024, col. 1, parag. 1, lines 4-6). Aβ is the modulator of integrin activity as the specification discloses that such modulators include A/β peptide (specification, page 19, parag. 0065, lines 1-4).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). Harris teaches detection of Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices (page 10367, col. 1, parag. 5, lines 1-5). Harris-White offer motivation in stating the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14).

Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the analysis of Matter et al using the hippocampal brain slice

assay of Harris-White given the motivation of Harris-White that the brain slice assay is more reflective of the in vivo situation than cultured cells.

Claims 1, 13-15, 59 and 69-71 rejected under 35 U.S.C. 103(a) as being unpatentable over Matter et al (1998) Journal of Cell Biology 141, pp. 1019-1030 in view of Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Matter teaches the deposition returned to control levels in the presence of an anti-α5 antibody (page 1024, col. 1, parag. 1, lines 4-6). Matter further teaches the peptide RGD and GRGDSP inhibited Aβ binding to the cell (page 1023, col.1, parag. 1, lines 23-33).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). Harris teaches detection of Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ1-40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Harris-White offer motivation in stating the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14).

Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the antibody and peptide studies described in Matter using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Claims 1, 19, 59 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hab et al (1998) Journal of Biolog. Chem. 273, pp. 13892-13897 in view of Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Hab teaches the expression of ApoE isoforms in combination with either an APP7562 haloprotein or an APP truncation lacking the Aβ sequence in COS (page a13896, col. 1,

parag. 2, lines 1-6). The results of these studies demonstrate binding of ApoE to the N-terminus of APP (page 13897, bridg. parag.).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). Harris teaches detection of Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ1-40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Harris-White offer motivation in stating the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14).

Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the apoE studies described in Hab using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Reynolds, SPE of AU 1632 whose telephone number 703-305-4051. The examiner can normally be reached on M-Th.

Should inquiries be made on or after January 12, 2004, the examiner's phone number will be 571-272-0727. Deborah Reynolds will be reached at 571-272-0734.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 for regular and After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

December 12, 2003